Acute kidney injury

Marlies Ostermann, Nuttha Lumlertgul, Rachel Jeong, Emily See, Michael Joannidis, Matthew James

Acute kidney injury (AKI) is a common, heterogeneous, multifactorial condition, which is part of the overarching syndrome of acute kidney diseases and disorders. This condition's incidence highest in low-income and middle-income countries. In the short term, AKI is associated with increased mortality, an increased risk of complications, extended stays in hospital, and high health-care costs. Long-term complications include chronic kidney disease, kidney failure, cardiovascular morbidity, and an increased risk of death. Several strategies are available to prevent and treat AKI in specific clinical contexts. Otherwise, AKI care is primarily supportive, focused on treatment of the underlying cause, prevention of further injury, management of complications, and short-term renal replacement therapy in case of refractory complications. Evidence confirming that AKI subphenotyping is necessary to identify precision-oriented interventions is growing. Long-term follow-up of individuals recovered from AKI is recommended but the most effective models of care remain unclear.

Lancet 2025; 405: 241–56

Department of Critical Care, King's College London, Guy's and St Thomas' NHS Foundation Trust, London, UK (M Ostermann PhD); **Excellence Centre for Critical Care Nephrology, Division of Nephrology, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand** (N Lumlertgul PhD); **Division of Nephrology, Department of Medicine** (R Jeong MD), **Department of Critical Care Medicine** (R Jeong), **Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; Departments of Intensive Care** (E See PhD), **Department of Nephrology** (E See), **Royal Melbourne Hospital, Melbourne, VIC, Australia; Department of Critical Care, University of Melbourne, Melbourne, VIC, Australia** (E See); **Division of Emergency Medicine and Intensive Care, Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria** (M Joannidis MD); **Division of Nephrology, Department of Medicine** (M James PhD), **Department of Community Health Sciences** (M James), **O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada**

Correspondence to:
Prof Marlies Ostermann, Guy's and St Thomas' NHS Foundation Trust, Department of Critical Care, London SE1 7EH, UK
marlies.ostermann@gstt.nhs.uk

Introduction

Acute kidney injury (AKI) is a multifactorial condition affecting 10–15% of hospitalised patients and more than 50% of patients in the intensive care unit (ICU).[1,2] Global estimates of the incidence of AKI in the last 15 years varied, with population-based data ranging from 114 to 174 people per 10 000 person-years, or a total of about 13·3 million patients, worldwide in 2017.[1,2] The incidence of AKI is highest in low-income and middle-income countries due to endemic diseases, contaminated water, and sociocultural factors.[1] Evidence is emerging that AKI is associated with a high risk of serious short-term and long-term complications, affects organs other than the kidney, contributes to increased health-care costs, and requires subphenotyping to enable personalised management.[3]

Definition of AKI and acute kidney diseases (AKD)

In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI established a harmonised definition and staging system for AKI that has since been extensively implemented within clinical practice, research, and public health initiatives (table 1).[4] The KDIGO guidelines placed AKI within an overarching syndrome of AKD, defined by serum creatinine, urine output and estimated glomerular filtration rate (eGFR), and structural criteria for kidney damage present for less than 3 months (figure 1, table 1).[6] Within this framework, AKI is defined by a duration of up to 7 days. AKI is part of AKD, but AKD might occur without AKI. In fact, epidemiological data suggest that AKD without AKI is more prevalent than AKD with AKI. Similar to AKI, AKD is associated with an increased risk of death and development or progression of chronic kidney disease (CKD).[7] Conceptually, AKD, AKI, and CKD are interlinked by their relationship with one another and by their criteria, complications, and outcomes.[5] Use of both urine output and serum creatinine criteria improves the sensitivity of detection of AKI and refines prognostic estimates of risk for renal replacement therapy (RRT) and mortality.[8,9]

Epidemiology of AKI and AKD

AKI and AKD represent substantial health challenges worldwide, affecting patients in both hospital and community settings across diverse socioeconomic contexts (figure 2). Among studies that applied the KDIGO creatinine-based AKI definition in hospital settings, a meta-analysis of global studies reported a pooled incidence of AKI of 22% in adults and 34% in children.[10] Duration and trajectory of AKI are also highly associated with mortality.[11] Persistent AKI (>48 h) is associated with higher morbidity and mortality, and an increased risk of progression to AKD and CKD than transient AKI (≤48 h).[5]

In high-income countries, AKI is particularly common in: critically ill patients; individuals with sepsis, hypotension, or hypovolaemia; patients who had undergone a major surgery; or patients with nephrotoxic medication exposures. In low-income and middle-income countries, AKI and AKD are most frequently caused by: acute illnesses in the community; environmental factors leading to heat stress and dehydration; infections such as malaria, dengue fever, diarrheal illnesses; and exposure to venoms and poisons.[12] A population-based study applying the KDIGO AKD criteria revealed an incidence of AKD without AKI of 3·8 per 100 adults tested, making this condition less common than CKD (10·6 per 100 adults tested), but more common than AKI (1·4 per 100 adults tested).[7] 77% of patients with AKD were

Search strategy and selection criteria

Data for this Review were identified by searches of PubMed and MEDLINE for original research papers, narrative reviews, systematic reviews, and meta-analyses, published between May 24, 2004, and June 30, 2024. Search terms used were: "acute kidney injury", "acute renal failure", and "renal replacement therapy". We gave preference to citations from the last 5 years published in English. However, we included older papers when studies from the last 5 years were not available. Additional references were selected from relevant articles and textbook chapters.

SHOUT
SHARE
IT

	Functional criteria	Structural criteria
NKD	GFR ≥60 mL/min per 1·73 m²; stable serum creatinine.	No kidney damage.
AKI	Serum creatinine increase by ≥0·3 mg/dL (≥26·5 umol/L) within 48 h, or increase ≥1·5 times baseline known or presumed to have occurred within the previous 7 days; or urine output <0·5 mL/kg per h for 6 h. AKI stage 1: serum creatinine 1·5–1·9 times higher than baseline within 7 days, or ≥0·3 mg/dL (≥26·5 umol/L) increase in 48 h or less, or urine output <0·5 mL/kg per h for 6–12 h. AKI stage 2: serum creatinine 2·0 to 2·9 times higher than baseline, or urine output <0·5 mL/kg per h for ≥12 h. AKI stage 3: in patients who are 18 years or older, serum creatinine increase ≥3·0 times baseline, or increase in serum creatinine to ≥4·0 mg/dL (≥353·6 umol/L), or urine output < 0·3mL/kg per h for ≥24 h, or anuria for ≥12 h, or initiation of RRT independent of serum creatinine concentration. In patients younger than 18 years, decrease in eGFR to <35 mL/min per 1·73 m², or urine output <0·3mL/kg per h for ≥24 h, or anuria for ≥12 h, or initiation of RRT independent of serum creatinine concentration.	No criteria established.
AKD	AKI, or GFR <60 mL/min per 1·73 m² for <3 months, or decrease in GFR by ≥35%, or increase in serum creatinine by >50% for <3 months. No AKD staging criteria established.	Markers of structural damage present for <3 months.
CKD	GFR <60 mL/min per 1·7m² for ≥3 months. CKD staging: GFR categories.	Kidney damage for ≥3 months. ACR categories.

ACR=albumin-to-creatinine ratio. AKD=acute kidney disease. AKI=acute kidney injury. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. GFR=glomerular filtration rate. NKD=no kidney disease. RRT=renal replacement therapy.

Table 1: **Kidney disease improving global outcomes criteria for kidney disease**

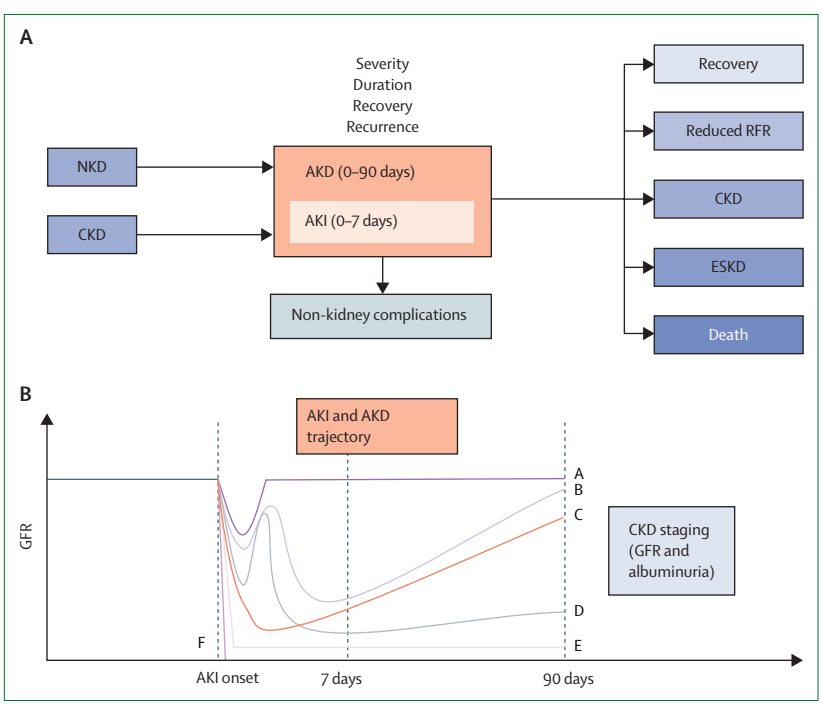


Figure 1: **AKI within the continuum of acute kidney disease and chronic kidney diseases**
(A) Patients might have NKD or CKD at baseline. After the onset of acute deterioration of kidney function, patients might have AKI lasting for up to 7 days or AKD lasting for up to 3 months. The trajectory and prognosis of AKI are characterised by the severity, duration (persistent *vs* transient), degree of recovery, and recurrence. Kidney function might recover, or the patient might have reduced RFR, progress to CKD (ie, lasting for more than 3 months) or ESKD, or die. Patients with AKI and AKD are also at risk of non-kidney complications (eg, cardiovascular events, stroke, fracture, infection, malignancy, gastrointestinal bleeding, and reduced quality of life). (B) Examples of GFR trajectories in AKI and AKD. Lines on the graph represent: A—mild and transient (<48h) AKI with sustained recovery; B—mild and transient AKI with recurrence then recovery; C—severe and persistent (≥48h) AKI with late recovery; D—moderate and transient AKI with recurrence without recovery; E—severe persistent AKI without recovery; and F—death after severe AKI. After 90 days, kidney disease is assessed using CKD staging by glomerular filtration rate and albuminuria. Figure adapted from paper by Kellum and colleagues.[5] AKD=acute kidney disease. AKI=acute kidney injury.CKD=chronic kidney disease. ESKD=end-stage kidney disease. GRF=glomerular filtration rate. NKD=no kidney disease. RFR=renal functional reserve.

identified from outpatient lab testing. AKD, with or without AKI, has been associated with increased risk of incident CKD, kidney failure treated with RRT, and death.[13,14]

AKI diagnostics

Traditional investigations

Creatinine is eliminated by the kidneys, and under steady-state conditions, urinary excretion equals creatinine production. As markers of kidney function, both serum creatinine and urine output have limitations that warrant recognition (panel). Creatinine clearance is the volume of blood plasma cleared of creatinine per unit time. This creatinine clearance value can be measured by determining the creatinine concentration in a specified urine collection and contemporary measurement of serum creatinine concentration. Creatinine clearance includes the creatinine that is freely filtered by the glomeruli and creatinine that is secreted by the peritubular capillaries. Thus, creatinine clearance over-estimates the GFR by approximately 10–20%. Despite the margin of error, creatinine clearance is an accepted method for measuring GFR. Repeated 4 h urine collections for creatinine clearance measurement in critically ill patients have been shown to allow earlier detection of AKI, and therefore better opportunities to control progression and recovery compared with the use of serum creatinine alone.[15]

In situations when creatinine concentration changes rapidly, the non-steady-state kinetic estimated GFR based on rate of creatinine production, initial serum creatinine, volume of distribution, and change over time, has been shown to be complementary to KDIGO AKI severity stages.[16] However, determining rate of creatinine production and volume of distribution is challenging in clinical practice.

Albuminuria is a marker of glomerular and endothelial disease; proteinuria in the absence of albuminuria is a marker of increased production (eg, light chain proteinuria) or impaired tubular reabsorption of low molecular weight proteins. The urine albumin-to-creatinine ratio (uACR) and protein-to-creatinine ratio provide quantitative assessment measures that account for urine concentration. However, urine creatinine excretion is decreased in AKI, which can falsely elevate uACR and protein-to-creatinine ratio.

Microscopic examination of the urine sediment for renal tubular epithelial cells, granular casts, and cellular casts helps diagnose specific parenchymal kidney diseases causing AKI. High interoperator variability in identifying cellular casts has been reported, even among trained nephrologists, but the identification of granular casts appears to be more consistent.[17]

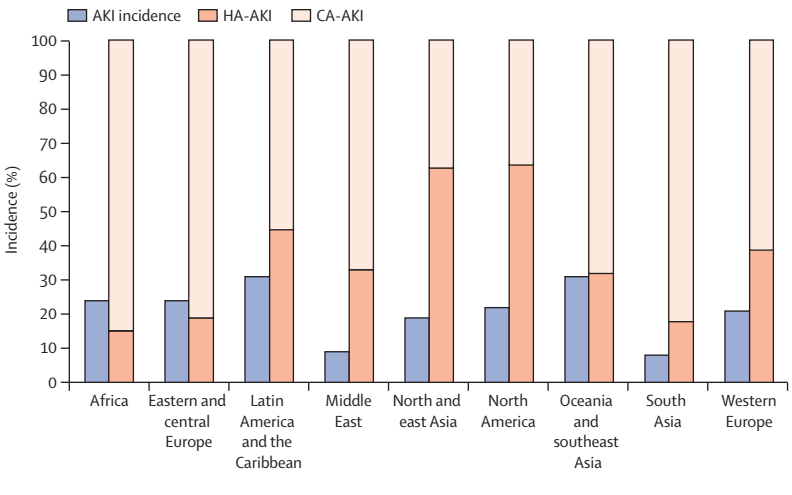
Furosemide stress test

The effectiveness of furosemide depends on tubular function. Therefore, the diuretic response after diuretic administration can be viewed as an indicator of tubular integrity. The furosemide stress test is a diagnostic tool, which involves the administration of 1 mg/kg of intravenous furosemide (or 1·5 mg/kg for patients with previous diuretic therapy). In critically ill adults with AKI, a urine output of <200 mL within 2 h had a sensitivity and specificity of 87% and 84%, respectively, for the progression to AKI stage 3.[18]

Imaging

Imaging studies are usually done to rule out urinary tract obstruction and assess kidney morphology and size. Point of care ultrasound has been shown to accurately detect hydronephrosis, evaluate intravascular filling, diagnose congestion, and be useful to monitor fluid and diuretic therapy. Some causes of urinary tract obstruction, such as retroperitoneal fibrosis and malignancy, might present without hydronephrosis and require pyelography or CT imaging for diagnosis. Similarly, dilatation of the urinary tract without obstruction might be observed after relief of obstruction with vesicoureteral reflux, after massive diuresis, and during pregnancy.

Doppler ultrasound of intrarenal venous flow is an emerging, non-invasive imaging technique to assess renal congestion. This method also allows to measure the renal resistive index to quantify the degree of vascular and renal parenchymal disease. Ultrasound imaging is operator-dependent, prone to substantial inter-observer variability, and not routinely available. Advanced multiparametric MRI allows multiple quantitative measures of kidney morphology, tissue microstructure, oxygenation, blood flow, and perfusion to be collected simultaneously and non-invasively.[19] However, these tools remain limited to the research setting.



	AKI incidence (%)	HA-AKI (%)	CA-AKI (%)
Africa	23·5	15	85
Eastern and central Europe	23·8	19	81
Latin America and the Caribbean	31·0	45	55
Middle East	9·0	33	67
North and east Asia	19·4	63	37
North America	22·3	64	36
Oceania and southeast Asia	31	32	68
South Asia	7·5	18	82
Western Europe	20·8	39	61

Figure 2: **Acute kidney injury (AKI) incidence by region**
Bar chart displaying incidence of AKI by region (blue), with stacked proportions of patients with Hospital-acquired (dark orange) versus Community-acquired (light orange) AKI by regions. Adapted from the International Society of Nephrology 0by25 Global Snapshot.[1] HA-AKI=hospital-acquired acute kidney injury. CA-AKI=community acquired acute kidney injury.

New molecular serum and urine biomarkers for AKI

New molecular blood and urinary biomarkers for AKI have been intensely studied in terms of their ability for prediction, prevention, diagnosis, and management of AKI. Growing evidence supports their clinical applications in select clinical scenarios.[20] Some biomarkers have received regulatory approval for clinical use and drug development (appendix pp 1–4).

See Online for appendix

Urinary dickkopf-3 is a kidney stress marker predictive of the risk of AKI, persistent kidney dysfunction, and RRT in patients receiving cardiac surgery.[21] Measurement of the two cell cycle arrest markers IGFBP7 and TIMP-2 has been approved by the FDA and in Europe for prediction of moderate to severe AKI. CCL14 is a biomarker of renal inflammation, indicating persistence of severe AKI.[22] NGAL is a damage biomarker that was approved by the FDA in 2023 for predicting severe AKI in children.[23] In patients with liver cirrhosis, this biomarker might help distinguish between acute tubular necrosis and hepatorenal syndrome, for which specific therapies are available.[24,25] Urinary tumour necrosis factor (TNF), and CXCL9 are inflammatory cytokines with apparent use for distinguishing acute tubulointerstitial nephritis from acute tubular necrosis, including identifying patients who

***Panel*: Limitations of urine output and serum creatinine for identification of acute kidney injury**

Urine output

- Risk of measurement error (eg, absence of a urinary catheter)
- Can be manipulated by diuretics
- Oliguria might be physiological (eg, during surgery)

Serum creatinine

- Affected by liver function, muscle mass and metabolism, recent (<6 h) meat-containing meal, and exogenous creatine intake
- Small increases can occur due to physiological and analytical variability, particularly with low baseline glomerular filtration rate (eg, chronic kidney disease)
- Can increase without true reduction in glomerular filtration rate, for instance in the setting of:
- Hemoconcentration (eg, diuresis)
- Inhibition of tubular secretion (eg, medications such as trimethoprim and cimetidine)
- Real increases might be concealed:
  - by fluid resuscitation and volume expansion
  - in case of malnutrition, liver disease, and muscle wasting during pregnancy, which is associated with physiological decrease of serum creatinine
- Some increases predict better long-term outcomes:
  - Renin–angiotensin–aldosterone inhibitors can increase serum creatinine due to renal afferent arteriole vasodilation; however, relatively small increases soon after initiation predict long-term preservation of kidney function
  - Sodium glucose-2 transporter inhibitors are associated with increases in serum creatinine concentration through tubuloglomerular feedback mechanisms leading to afferent arteriole constriction, yet improve cardiovascular and kidney outcomes and appear to lower the risk of acute kidney injury

might benefit from steroid therapy.[26,27] Cystatin C is a functional biomarker that, unlike creatinine, is not influenced by muscle loss and might therefore improve the accuracy of GFR estimation after critical illness.[28]

Panels of molecular biomarkers, such as plasma TNFR1 and TNFR2, urinary MCP1, uromodulin, and EGF measured 3 months after AKI have been associated with progression of CKD and cardiovascular events,[29,30] and have potential for guiding long-term renal and cardiovascular management but further research is needed. In 2019, the Acute Disease Quality Initiative (ADQI) expert panel emphasised that biomarker testing should be informed by broader kidney health assessment, incorporating patient factors and exposures, and that validated biomarker tests had a role to identify patient populations who are likely to benefit from specific interventions.[31]

Pathophysiology of AKI

The causes of AKI are diverse, and the pathological conditions associated with AKI are heterogeneous and complex.[32] Preclinical studies have highlighted that different aetiologies of kidney injury elicit divergent responses at the molecular, cellular, and functional levels, simultaneously or in sequence (figure 3).[33]

Common types of AKI

Sepsis-associated AKI

Severe infection and sepsis are the most frequent aetiologies of AKI worldwide. AKI develops in about 70% of patients with sepsis and often progresses to AKI stage 3.[34,35] The term sepsis-associated AKI includes cases of sepsis-induced AKI, whereby the patient's response to sepsis causes kidney injury directly, and cases in which sepsis-associated factors (such as therapeutic interventions, including nephrotoxins) contribute.

Multiple pathophysiological mechanisms appear to simultaneously contribute to sepsis-associated AKI, including systemic and renal inflammation, altered microcirculatory and endothelial function, intra-renal shunting, complement activation, renin–angiotensin–aldosterone system (RAAS) dysregulation, mitochondrial dysfunction, and metabolic reprogramming.[35] Management consists of rapid control of the underlying infection, individualised haemodynamic and fluid resuscitation, and avoidance of further nephrotoxic insults.

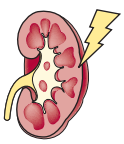
AKI post-major surgery

Postoperative AKI is defined when KDIGO AKI criteria are met within 7 days of an operative intervention.[36] Postoperative AKI occurs in approximately 15% of non-cardiac surgeries and 30–40% of cardiac surgeries, though rates vary depending on the type of surgery, patient risk factor profile, and whether urine output is included in the AKI diagnosis.[37]

The pathophysiology involves multiple mechanisms, including hypovolemia, vasodilation and decreased cardiac output secondary to anaesthetic drugs, and increased intra-abdominal pressure following induction of pneumoperitoneum. Systemic inflammation from surgical stress, large volume shifts, and nephrotoxin exposure also contribute. The AKI risk increases upon higher preoperative baseline proteinuria.[38]

Avoiding hypovolemia and hypotension before and during surgery is recommended, including avoidance of excessively restrictive fluid management.[36,39,40] Maintaining patients' systolic blood pressure close to their usual blood pressure during the intraoperative period was associated with a significantly lower risk of postoperative AKI.[41]

Until autumn of 2024, cessation of use of RAAS inhibitors before surgery was recommended. However, the Stop-or-Not[42] randomised controlled trial (RCT) including 2222 patients who were on RAAS inhibitors therapy for at least 3 months and scheduled to undergo a major non-cardiac surgery, showed that continuing



Microcirculatory dysfunction	Inflammation	Endothelial dysfunction	Tubular cell toxicity	Renal venous congestion	Mitochondrial dysfunction	Obstruction	Glomerular disease
• Altered vascular tone • Intrarenal and peri-glomerular shunting • Re-distribution of blood flow • Focal perfusion deficits	• Recruitment of leukocytes • Activation of inflammatory cells • Release of inflammatory mediators • Interstitial immune reaction	• Vasodilation • Increased vascular permeability • Formation of microthrombi • Flow disturbance	• Acute tubular injury or cell death • Inflammatory response • Tubuloglomerular feedback • Cell cycle arrest	• Compression of intrarenal veins • Intrarenal compartment syndrome	• Labile mitochondria • Altered mitochondrial function • Down-regulation of ATP consuming processes	• Intratubular, intra-luminal, or extrinsic obstruction	• Thrombotic microangiopathy • Autoimmune processes • Complement activation

Figure 3: **AKI pathophysiology**
Key pathophysiological mechanisms contributing to acute kidney injury. AKI=acute kidney injury.

RAAS inhibitors therapy before surgery did not increase the risk of postoperative AKI compared with a discontinuation strategy (11% in both groups). However, patients in the RAAS inhibitors continuation group had a significantly higher risk of intraoperative hypotension compared with patients in whom RAAS inhibitors therapy was discontinued (54% *vs* 41%). Thus, RAAS inhibitors can be continued perioperatively unless a particular concern for profound intraoperative hypotension exists.

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are increasingly prescribed to patients with diabetes, CKD, or heart failure. They can cause an initial rise in serum creatinine and a decrease in GFR which is usually temporary. The American Diabetes Association recommends to avoid SGLT2 inhibitors in severely ill patients and during prolonged fasting and surgical procedures.[43] However, the EMPEROR trial[44] showed that abrupt cessation of SGLT2 inhibitors had negative consequences.[45] Moreover, a meta-analysis of 13 SGLT2 inhibitors trials in patients on chronic SGLT2 inhibitors therapy for at least 6 months concluded that the overall risk of AKI with SGLT2 inhibitors compared with placebo was reduced by 23% (relative risk 0·77, 95% CI 0·7–0·84). Thus, discontinuation appears appropriate in cases of shock, metabolic acidosis, or severe urinary tract infection but continuation should be considered in patients with strong indications, for instance with severe heart failure.

In the setting of cardiac surgery, off-pump cardiopulmonary bypass, compared with on-pump, confers a benefit of lower incidence of postoperative AKI.[46,47] Further, perioperative intravenous amino acid infusion reduced the risk of postoperative AKI in a multicentre RCT published in 2024.[48] The association between perioperative non-steroidal anti-inflammatory drugs and AKI is unclear.[49]

Drug-associated AKI

Drug-associated kidney disease is estimated to account for 19–26% of all cases of AKI in hospitalised patients.[50] There are several different pathophysiological mechanisms that contribute to drug-associated AKI, including direct tubular injury, intratubular obstruction, microvascular alteration, and interstitial inflammation (ie, acute tubulointerstitial nephritis).[51,52] Since many medications are renally metabolised and eliminated, AKI is an important contributor to therapeutic interruptions and delay in diagnostic tests and interventions. Karimzadeh and colleagues[53] differentiate between drugs that cause: kidney dysfunction without damage (eg, RAAS inhibitors), damage without dysfunction (eg, vancomycin), both dysfunction and damage (eg, non-steroidal anti-inflammatory drugs), and neither dysfunction nor damage (eg, trimethoprim). Drugs that are not nephrotoxic but are renally cleared might accumulate in AKI and also cause harm (eg, β blockers, sedatives).

AKI in heart failure

Cardiorenal syndrome describes pathophysiological disorders of the heart and kidneys in which acute or chronic dysfunction in one organ induces acute or chronic dysfunction in the other.[54] Mechanisms include reduced effective circulating volume, renal venous congestion, activation of the sympathetic nervous system and RAAS, inflammation, and an imbalance in reactive oxygen species and nitric oxide production. AKI prevention and management focus on optimal management of heart failure and coronary artery disease.[55] During decongestion therapy, serum creatinine often rises. Studies have confirmed that ongoing diuretic therapy in volume-overloaded patients is associated with reduced mortality and a lower risk of rehospitalisation without causing kidney damage.[56,57] Withdrawing or

reducing diuretics during the decongestion therapy might be counterproductive.

AKI in liver disease

Among hospitalised patients with cirrhosis, up to 50% develop AKI. The risk of AKI increases to 80% in patients with cirrhosis admitted to the ICU.[25] Susceptibility to AKI varies across individuals depending on non-modifiable factors (eg, comorbidities), modifiable factors (eg, sepsis, nephrotoxic drugs), and factors related to liver disease (eg, ascites, decompensating events).

Hepatorenal syndrome describes a specific phenotype of renal dysfunction observed in patients with cirrhosis with clinically significant ascites. AKI in this context is the result of reduced renal perfusion through hemodynamic alterations in the arterial circulation, coupled with portal hypertension and splanchnic vasodilation, overactivity of the endogenous vasoactive system, and systemic inflammation. In 2023, representatives of ADQI and the International Club of Ascites proposed a change to the diagnostic criteria for hepatorenal syndrome-associated AKI. The experts recommended that hepatorenal syndrome-associated AKI be considered in patients with cirrhosis, ascites, and AKI, where intravascular volume status was deemed adequate and where there was no alternative explanation for AKI.[25] Routine administration of intravenous albumin for 48 h is no longer a requisite for the diagnosis of hepatorenal syndrome-associated AKI. The time window for evaluating the response to volume resuscitation (when indicated) should be within 24 h, to avoid fluid overload and ensure timely initiation of vasoconstrictor therapy. Terlipressin is considered the first-line agent in combination with 20–25% albumin. However, meta-analyses have shown comparative effects between norepinephrine and terlipressin for reversal of hepatorenal syndrome-associated AKI.[58] Close monitoring of volume status during treatment with terlipressin is recommended, including adjustment or discontinuation of therapy in case of volume overload or no response.

Pregnancy-associated AKI

Pregnancy-associated AKI is associated with maternal and neonatal morbidity and mortality.[59] Common causes are pre-eclampsia, sepsis, and haemorrhage. The presence of the fetal–placenta unit results in pathophysiological changes including haemodynamic, neurohumoral, immunological, vascular, and structural alterations.[60] Mechanical pressure from the gravid uterus and pregnancy-associated hormonal changes can lead to physiological dilatation of the urinary collecting system with reduced peristalsis, which increases the risk of urinary tract infections. Pre-eclampsia, eclampsia, and the syndrome of haemolysis, elevated liver enzymes, and low platelet count are pregnancy-specific syndromes resulting from placental dysfunction that can cause AKI. Individuals with known glomerulonephritis might experience flares during pregnancy.

An increase in renal plasma flow by 80% and in GFR by 50% leads to a natural decrease in serum creatinine by gestational age, which poses a challenge for pregnancy-associated AKI diagnosis (panel).[61] When feasible, serum creatinine, urinalysis, urine dipstick, or quantitative albuminuria obtained with uACR should be determined at the first encounter and repeated in patients with ongoing insult. In patients with serum creatinine higher than the reference concentrations or with an increase in serum creatinine above baseline, serial creatinine monitoring helps determining whether these individuals have AKI, AKD, or CKD. The role of new biomarkers in diagnosing and prognosticating pregnancy-associated AKI is unclear.[62]

Treatment of pregnancy-associated AKI is tailored by its specific cause. Fluid resuscitation is key to maintain renal and uteroplacental perfusion in case of hypovolaemia but should be done with caution in women with pre-eclampsia or cardiomyopathy owing to the risk of pulmonary oedema. In cases of pre-eclampsia, placental abruption, haemolysis, elevated liver enzymes low platelets syndrome, and acute fatty liver of pregnancy, delivery of the foetus should be considered to reverse maternal organ dysfunction.[63] Delivery might also be needed to remove the source of sepsis (eg, chorio-amnionitis). Specific AKI aetiologies, (eg, lupus nephritis, thrombotic thrombocytopenic purpura) might need treatment with immunosuppression or plasma exchange. There are fetal and maternal indications for RRT. The maternal indications do not differ from those of non-pregnant individuals.[64]

Risk assessment and prevention of AKI

AKI risk profiling is essential to inform tailored monitoring and preventive measures. Risk factors for AKI can be categorised into: comorbidities, exposures, processes of care, environmental, socioeconomic, and cultural factors. The effect of each factor on AKI risk varies by patient characteristics, health-care system, and resource availabilities. Modifiable (eg, dehydration, fluid overload, nephrotoxic drugs, and major surgery) and non-modifiable (eg, age, sex, ethnicity) factors affect AKI susceptibility and prognosis. Male sex is associated with an increased risk of AKI in preclinical models, but the evidence for sex differences in clinical risk and outcomes of AKI is mixed.[65]

Numerous aetiology-specific and procedure-specific risk prediction models and scores exist, in particular for patients undergoing cardiac surgery and percutaneous coronary intervention.[66–68] The renal angina index uses individual risk profiles and creatinine changes to predict severe AKI development in both children and adults.[69] Various biomarkers predict AKI occurrence, progression, RRT receipt, and clinical outcomes.[31] Measurement of renal functional reserve provides an assessment of the difference between resting GFR and stress GFR, which predicts the risk of AKI post-cardiac surgery.[70]

Clinical decision support systems analyse data from electronic health records in real-time to identify modifiable risk factors, predict or detect AKI early, and guide tailored interventions and follow-up.[71] AKI electronic alerts have been associated with increased documentation, nephrology referral, and discontinuation of medications but the benefits on patient-centred outcomes are inconsistent.[72–75]

Digital health tools, including telemedicine and wearable sensors and devices, offer opportunities for enhanced AKI care at individual, health-care system, and population levels.[76,77] A feasibility study in resource-limited areas showed that telemedicine, combined with educational programmes and a point-of-care kidney function test, could identify AKI early and inform management.[78] A clinical decision support system that combined renal angina index with a conditional urine NGAL measurement to guide RRT initiation in children was associated with shorter hospital stay, increased survival, and health-care cost savings.[23,79]

The general principles of AKI prevention are treatment of the precipitating factors and avoidance of further nephrotoxic insult.[4] Biomarker-guided implementation of an AKI care bundle has been shown to reduce the development of moderate-to-severe AKI after major cardiac and non-cardiac surgery.[80–83] A stepped-wedge, cluster RCT that used a clinical decision support system on contrast volume and hemodynamic-guided intravenous fluid targets, combined with an education programme, audit, and feedback showed a 2·3% absolute risk reduction in the incidence of contrast-associated AKI.[77]

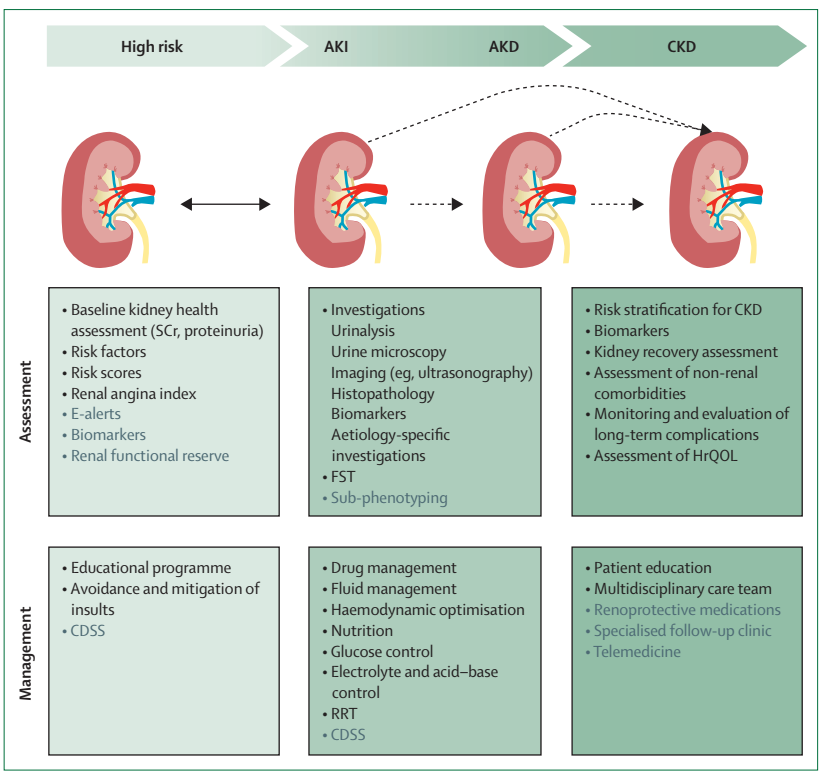


Figure 4: **Summary of the current evidence regarding the assessment and management of the AKI continuum from high-risk state to AKI, AKD, and CKD**

Grey text refers to investigations or therapies under investigation. AKD=acute kidney disease. AKI=acute kidney injury. CDSS=clinical decision support system. CKD=chronic kidney disease. FST=furosemide stress test. HrQOL=health-related quality of life. RRT=renal replacement therapy. SCr=serum creatinine.

Non-dialytic management of AKI

With a few exceptions (eg, immunosuppression for glomerulonephritis or acute tubulointerstitial nephritis, terlipressin for hepatorenal syndrome), management of AKI is primarily supportive, including treatment of the underlying cause, prevention of further injury, and management of complications of AKI (figure 4).

Drug management

Drugs that are directly toxic to the kidney should be avoided, withheld, or ceased when possible. Drug stewardship programmes help to rationalise nephrotoxic drug use, and therapeutic drug monitoring informs drug dosing and monitoring.[84] It is increasingly recognised that RAAS inhibitors can often be safely continued in the absence of hypotension or hyperkalaemia, especially in the context of cardiorenal syndrome.[85] Renally cleared drugs might accumulate, leading to systemic toxicity.

Fluid management

Both hypovolaemia and hypervolaemia are important determinants of kidney perfusion and influence AKI progression and recovery. In AKI, the goal of fluid administration is to achieve euvolemia and to improve cardiac output and kidney perfusion without causing or worsening fluid overload. The volume of fluid needed varies depending on the type of illness and comorbidities.

Overall, buffered crystalloids might confer a mortality benefit compared with 0·9% saline, except for patients with traumatic brain injury.[86] Albumin does not reduce the risk of severe AKI in sepsis but is recommended for patients undergoing large volume paracentesis and patients with spontaneous bacterial peritonitis or hepatorenal syndrome treated with terlipressin.[87] Synthetic colloids increase the risk of RRT and should be avoided.[88] Loop diuretics can be used to treat hypervolaemia but have no other role in the treatment of AKI.[89]

Haemodynamic management

Prompt reversal of hypotension to a pressure higher than the threshold for renal autoregulation might prevent AKI progression and enhance recovery.[90] An initial mean arterial pressure target of 65 mmHg can be set for most patients. A beneficial effect of higher mean arterial pressure targets on renal function in patients who had been hypertensive can be observed but the results are not consistent.[91–93] The mean arterial

pressure target should be individualised, based on pre-existing blood pressure results and markers of organ perfusion.[93]

In general, fluids are used to correct hypovolaemia, vasopressors are required in case of vasoplegia, and inotropes are indicated to improve cardiac output. Norepinephrine is recommended as the first-line vasopressor in AKI.[4] However, given the differences in receptor distributions within the kidneys, other vasoconstrictors might be of use in some AKI sub-phenotypes.[94] A post-hoc analysis of the ATHOS 3 trial[95] showed that patients receiving RRT had improved survival and earlier liberation from RRT if randomly assigned to angiotensin II.

Supportive measures

The role of cation exchange resins to prevent hyperkalaemia in patients with AKI has not been confirmed. Metabolic acidosis occurs commonly in AKI but rarely requires treatment, unless severe. Anaemia should be corrected to a target haemoglobin of more than 75 g/L, but there is no evidence that a higher haemoglobin target is beneficial.[96,97] AKI can induce platelet dysfunction, leading to an increased risk of clinically significant bleeding.

Nutritional support is an important component of managing patients with AKI. In the absence of high-level evidence to inform nutritional therapy, calorie and protein intake for AKI patients should be prescribed as for other hospitalised patients, but high protein delivery might increase mortality in critically ill AKI patients.[98,99] Restrictions on potassium, phosphate, and sodium intake apply to most patients with AKI and hyperglycaemia should be avoided. Micronutrient supplementation is recommended for patients receiving RRT.[99]

Renal replacement therapy

RRT constitutes a process of care requiring regular evaluation, monitoring, and reassessment (figure 5).

Timing

Urgent indications for RRT include medically refractory hyperkalaemia, metabolic acidosis, fluid overload with pulmonary oedema, and uremic complications. In clinical practice, they are rare. Relative indications are more common but defined with less precision. In the absence of urgent indications, RCTs from 2016 to 2020 support a watchful waiting approach (figure 5).[100–103] The ELAIN trial showed improved survival when RRT was started at AKI stage 2 compared with AKI stage 3 in a cohort of predominantly surgical patients at a single centre.[103] Three subsequent multicentre RCTs (AKIKI, IDEAL-ICU, and STARRT-AKI) showed no benefit with early initiation, although different criteria for early and late RRT were applied.[100–102] In these trials, deferred initiation reduced the utilisation of RRT by about 40% on average. Further, the STARRT-AKI trial showed a higher rate of RRT dependence at 90 days in patients randomly assigned to accelerated RRT initiation group.[102] The AKIKI-2 trial showed that RRT deferral for patients with AKI stage 3, oliguria for more than 72 h, and blood urea nitrogen of more than 140 mg/dL, however, was associated with increased 60-day mortality and no difference in RRT-free days.[104] The balance of evidence from these RCTs indicates that initiation of RRT without an AKI-related urgent indication does not improve clinical outcomes.[105]

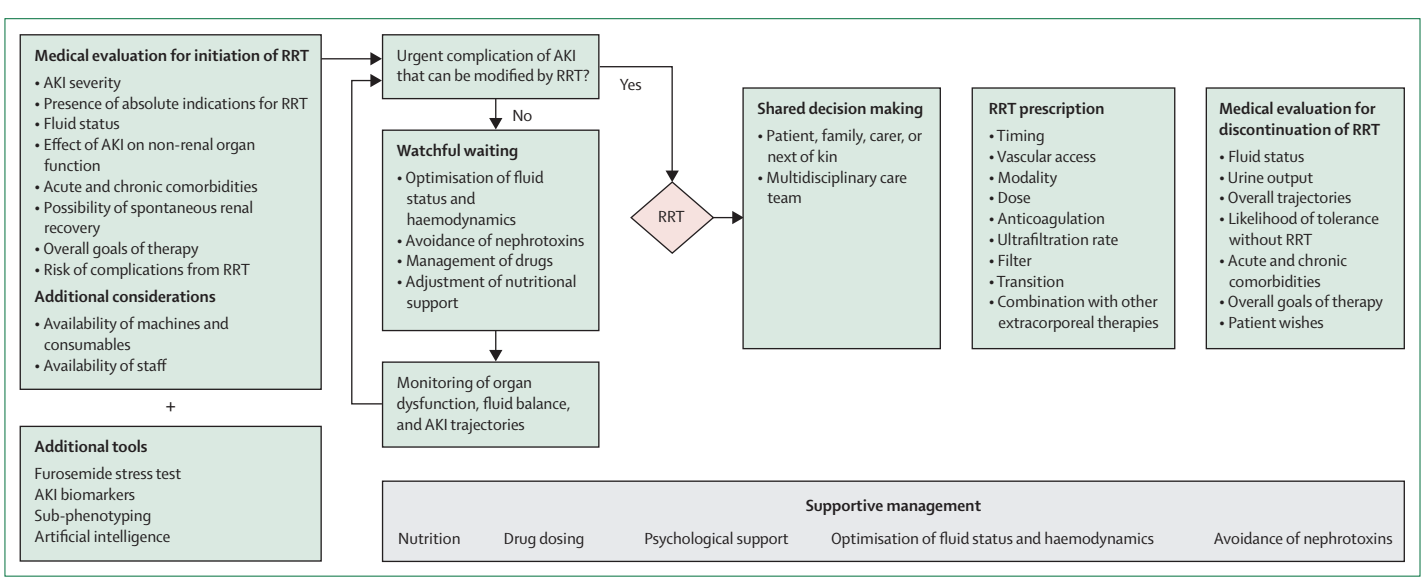


Figure 5: **Processes of RRT care**
AKI=acute kidney injury. RRT=renal replacement therapy.

Modality

The spectrum of RRT therapies includes continuous RRT, conventional intermittent haemodialysis, and prolonged intermittent RRT which includes slow extended dialysis, and acute peritoneal dialysis.[106] Despite some apparent differences related to haemodynamic tolerance, RCTs have not shown a significant survival difference between modalities.[107] The final choice is often informed by patient factors, clinician expertise, and resource availability. Continuous RRT, and where applicable peritoneal dialysis, might be preferential to conventional intermittent haemodialysis for patients with acute brain injury or increased intracranial pressure. A secondary analysis of the STARRT-AKI trial[108] concluded that continuous RRT as the initial modality was associated with a lower risk of death or dialysis dependency at 90 days. Intermittent modalities offer the opportunity to allow active mobilisation and improved sleep quality. Thus, there is often a transition from continuous RRT to intermittent therapies when patients are physiologically and metabolically able to tolerate fluctuations in fluid status and the risks of cerebral oedema have resolved.[109] Acute peritoneal dialysis is predominantly applied in resource-limited settings and in children.[110]

Dose

Intensity of RRT was investigated in the ATN and the RENAL trials,[111,112] leading to current recommendations to prescribe a dose of 25–30 mL/kg per h for continuous RRT and a weekly urea removal times treatment duration divided by the volume of distribution for urea of 3·9 for intermittent haemodialysis. The recommended dose for prolonged intermittent RRT is less clearly established. Uremic milieu might promote kidney repair after injury, implying that lower doses of RRT might be beneficial.[113] Clinical trials investigating lower doses are ongoing.

Ultrafiltration

There is a balance between reversing fluid overload rapidly and the risk of intradialytic hypotension if fluid is removed too fast. Based on secondary analyses of the ATN and RENAL trials, moderate fluid removal at 1·01–1·75 mL/kg per h appears to be safe.[111,112,114]

Anticoagulation

Worldwide, unfractionated or low molecular weight heparin are the most used anticoagulants and are recommended for patients receiving intermittent haemodialysis or prolonged intermittent RRT.[4] For continuous RRT, regional citrate anticoagulation is increasingly used after data showing better filter patency and less bleeding complications.[115,116]

Discontinuation

Creatinine and other uremic toxins are removed during RRT and are not reliable indicators of renal recovery. Based on large cohort studies, a spontaneous urinary output of more than 500 mL/day, or 2·4 L/day with the use of diuretics, are widely accepted criteria for considering discontinuation, provided there are no ongoing or new indications for RRT.[117] The role of renal biomarkers to guide decision making is under investigation. Diuretic use does not hasten liberation from RRT.[118]

Supportive strategies

Drug dosing is particularly challenging during RRT, especially during periods of transition of therapy, recovery of kidney function, and if additional types of extracorporeal therapies are needed. Both underdosing and overdosing of medications, including of antimicrobial drugs, have been reported.[119] Novel dosing strategies, including therapeutic drug monitoring and advanced pharmacokinetic modelling are being explored to optimise drug dosing during RRT.

AKI subphenotyping

Molecular approaches in preclinical research, including analysis of gene and protein expression, localisation of gene transcripts, and measurement of biomarkers, have highlighted important heterogeneity in AKI, which is not captured by the current AKI definition. Even within the spectrum of acute tubular injury (ATI), there is less than 10% overlap in genetic expression between ATI from different injuries (eg, hypotension, renal artery ligation, and sepsis).[33]

Recognition is growing for the fact that AKI subphenotyping with the use of new and conventional biomarkers, along with selected clinical features, is required to identify reproducible subpopulations that might respond differently to treatment, enabling personalised and precision-oriented management.[120–122] For instance, among patients with acute tubulointerstitial nephritis, individuals with high urinary interleukin-9 concentrations benefitted from corticosteroid therapy.[27] Separately, in a series of post-hoc analyses of patients with sepsis and acute respiratory distress syndrome, a distinct AKI subphenotype based on biomarkers of endothelial dysfunction and soluble tumour necrosis factor receptor 1 was identified that benefited from treatment with vasopressin and norepinephrine (compared with norepinephrine alone) in septic shock.[123] A strategy of using existing data, including data stored within electronic health records, supplemented by new biomarkers, offers promise for personalised AKI care.

Organ crosstalk

The term organ crosstalk describes the negative interference of a failing organ in other organs. There are several reasons for why AKI can lead to dysfunction of other organs.[124,125] First, AKI and multi-organ failure might represent the effect of a common underlying disease (sepsis or cardiogenic shock). Second, after the initial trigger of AKI, intrarenal inflammation might lead to the release of inflammatory mediators and activated

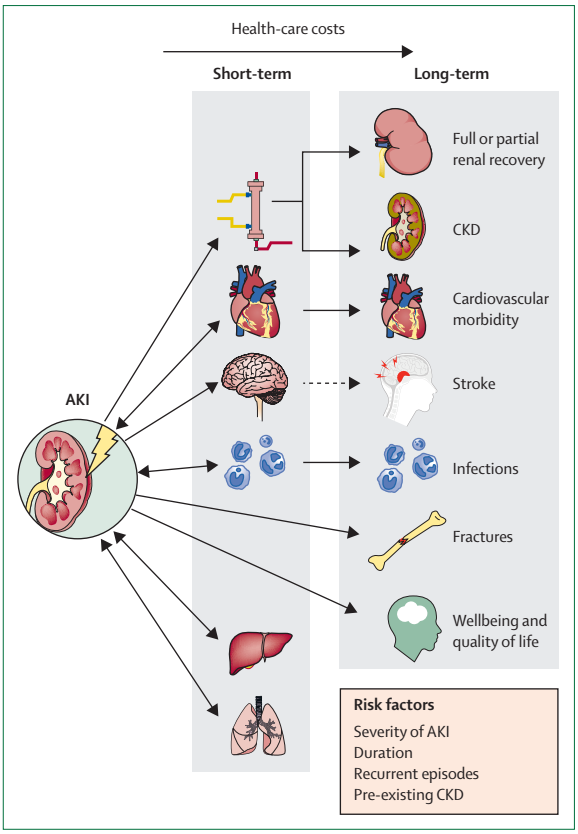


Figure 6: **Short-term and long-term complications after AKI**
AKI=acute kidney injury. CKD=chronic kidney disease.

immune cells into the systemic circulation, causing distant organ dysfunction. Finally, organ dysfunction might occur because of uraemia, fluid overload, acid–base disbalance, or potential complications of interventions, such as RRT.

Crosstalk exists between the kidneys and the heart, lung, liver, gut, and the brain, but also the immune system, with evidence of AKI-induced immunosuppression resulting in a higher susceptibility to secondary infections. These interactions likely contribute to the increased morbidity and mortality that is associated with AKI.

Outcomes after AKI

The outcomes of AKI and AKD vary substantially based on patient factors, duration of AKI and AKD, and health-care infrastructure.[126] Mortality rates with AKI have been reported to be 24% in adults and 14% in children, and are inversely related to the income of countries and percentage of gross domestic product applied to health expenditure.[9] Mortality rates are higher in critically ill patients and individuals treated with RRT.[1]

Patients recovered from AKI often face long-term complications, including CKD, dialysis dependence, and increased cardiovascular risk (figure 6).[127,128] In high-resource countries, the economic burden of AKI is substantial, with long hospital stays and the need for ICU admission. Ethnicity, income, education, access to health care, sociocultural factors, and social deprivation have been reported to contribute to poor outcomes.[129,130]

Renal recovery

Although there is no consensus on the criteria for renal recovery, it is often defined as complete or partial. Complete recovery is defined by return of serum creatinine to baseline concentration and partial recovery means that AKI has resolved but serum creatinine concentration has not returned to baseline.[131,132] AKI reversal can be categorised as rapid (resolving within 48 h) or delayed (when the condition persists beyond 48 h). In a retrospective cohort study[11] of 16 968 critically ill patients with stage 2 or 3 AKI, 41% of patients had not fully recovered kidney function at the time of hospital discharge. Of these patients, 26% had no AKI reversal at any point, and 15% had reversal but relapsed without subsequent recovery.

The presence or absence of renal recovery and its timing have prognostic implications. Compared with recovery within 10 days, later recovery is associated with an increased risk of a sustained decline in eGFR or kidney failure.[133] A prospective cohort study showed that those with non-resolving AKI, compared with resolving AKI, had a 51% higher risk of major adverse kidney events.[134] Creatinine-based eGFR might overestimate renal recovery due to factors related to hospitalisation and critical illness, such as loss of muscle mass.

AKI also carries a risk for future recurrent AKI. In one study,[135] a quarter of hospitalised patients with AKI experienced recurrent AKI requiring hospitalisation within 12 months of discharge, with a median time to recurrent AKI of 64 days. Recurrent AKI is associated with an increased risk of death.[136]

The risk of CKD and kidney failure increases with greater KDIGO AKI stage in a graded way.[137,138] Much of the risk of long-term decline in kidney function in patients with AKI stage 1 and 2 might be accounted for by pre-existing kidney problems and proteinuria.[139] For 37% patients hospitalised with AKI, a major adverse kidney event occurred within the first year,[140] whereas in critically ill patients with AKI, 94% experienced a major adverse kidney events by 3 years.[141]

The risk of proteinuria, a marker and risk factor for CKD progression, is increased after AKI and there appears to be a positive correlation with frequency and severity of AKI.[142] In the ASSESS-AKI study,[143] for each doubling of uACR, the hazard ratio for kidney disease progression was 1·53 (95% CI 1·45–1·62).

Mortality

AKI individuals recovered from AKI experience an increased risk of short-term and long-term mortality. This increase is particularly large for individuals who

survived a stay in the ICU.[140] The most common causes of death after AKI are cardiovascular disease and cancer.[144]

Quality of life

Several studies have reported lower health-related quality of life in individuals recovered from critical illness and severe AKI.[145] Frailty is also common in individuals recovered from AKI, especially in those with more severe AKI. In children who survived an episode of AKI, memory deficits and learning impairments have been reported.[145]

Major limitations of interpreting health-related quality of life results across studies are the confounding effect of frailty and heterogeneity in the timing of assessment, assessment tools, patient population, and duration of follow-up. Most individuals who recovered from AKI who had received RRT viewed their health-related quality of life as acceptable and expressed a wish to receive similar treatments again.[146]

Non-renal comorbidities

The risk of major adverse cardiac events, heart failure, coronary events, and hypertension is increased in AKI individuals who recovered.[147–149] Analysis of a national database in Taiwan revealed a higher incidence of stroke and increased severity of stroke events in individuals recovered from dialysis-requiring AKI compared with matched controls without AKI.[149] AKI requiring dialysis has also been associated with the development of dementia.[150] Furthermore, associations between AKI and an increased long-term risk of severe sepsis, upper gastrointestinal haemorrhage, fractures, and malignancy have been reported.[151–154]

AKI aftercare

Patient transition from hospital to home after AKI requires continuity of care in the community (figure 4). The 2012 KDIGO guidelines suggest that patients should be evaluated 3 months after AKI for resolution, new onset, or worsening of pre-existing CKD.[155] However, effective models of care to improve hospital-to-home transitions and long-term outcomes remain unclear. Studies have reported better processes of care and outcomes associated with nephrology specialist follow-up and structured post-AKI clinics, but follow-up with specialists remains challenging to coordinate.[156–158] Patients have described prioritisation of other health conditions over their kidney disease, low awareness of AKI as a potential long-term health issue, and anxiety from competing health demands as challenges.[159] Further, health-care providers often perceive AKI as a complex condition to manage, at times requiring clinical decisions that conflict with the treatment of other comorbidities.[160]

Research in the last 8 years suggests that biomarker panels and risk prediction models to risk stratify patients for progression to advanced CKD after AKI could improve the appropriateness and efficiency of follow-up by targeting

	Objective	Population	Main outcomes and endpoints	Positive effects for practice
BipAK-2[168] **(NCT04647396)**	RCT to explore whether timely application of an AKI care bundle in patients who are kidney biomarker positive after major surgery prevents AKI	Patients undergoing major surgery and at high risk for postoperative AKI.	Primary endpoint of incidence of AKI stage 2 or 3 within 72 h after surgery. Secondary endpoints include any AKI, need for RRT, duration of RRT, renal recovery, mortality, LOS, and MAKE	Strategy to prevent AKI after major surgery and its consequences
PREVENTS-AKI (NCT05468203)	RCT to test the effect of dapagliflozin versus placebo upon critically ill patients' risk of developing severe AKI	Adult ICU patients at high risk of AKI.	Primary outcome of doubling of serum creatinine, initiation of RRT, or death Secondary outcomes include mortality, use of vasopressors, and mechanical ventilation	Possible strategy to prevent or mitigate AKI during critical illness
Artemis (NCT05746559)	RCT to investigate the role of ravulizumab to protect patients with CKD from AKI after cardiac surgery-associated AKI	Adult patients with CKD undergoing cardiac surgery	Primary outcome of MAKE 90. Secondary outcomes include mortality, need for RRT and AKI free days	Possible therapy to prevent deterioration of kidney function in CKD patients undergoing cardiac surgery
CLEAR-AKI (NCT05996835)	RCT to investigate the role of TIN-816 (an ATP modulator) in sepsis-associated AKI	Critically ill adult patients with sepsis-associated AKI	Primary outcome of endogenous creatinine clearance from day 1 to day 8. Secondary outcomes include MAKE, use of RRT, survival, and change of SOFA score	Possible therapy to facilitate renal recovery in critically ill patients with sepsis-associated AKI
Development and external validation of a machine learning model for prediction of persistent AKI stage 3[169]	Machine learning analysis to develop and validate a real-time model able to accurately predict persistent AKI in the ICU	Adult patients in ICU with AKI stage 2 or 3	Primary endpoint of ability to predict AKI stage 3 lasting for at least 72 h when in the ICU	Prediction of persistent AKI has potential to initiate strategies that improve AKI outcomes
COPE-AKI[164] (NCT05805709)	RCT comparing a multimodal process-of-care intervention to usual care after moderate to severe AKI	Adult patients with AKI stage 2 or 3 and evidence of persistent AKI	Primary outcome of hospital-free days through day 90. Secondary outcomes include MAKE at 90, 180, and 365 days, recurrent AKI, and quality of life	Information to guide follow-up care of AKI, including education and medication reconciliation

AKI=acute kidney injury. CKD=chronic kidney disease. ICU=intensive care unit. LOS=length of stay. MAKE=major adverse kidney event. RCT=randomised controlled trial. RRT=renal replacement therapy. SOFA=Sequential Organ Failure Assessment.

Table 2: **AKI research in progress (selected studies)**

enhanced follow-up care strategies to patients most likely to benefit.[161–163] Patient education, improved communication strategies about AKI to community-based health-care providers, and clear guidance on intensity of clinical follow-up and therapeutic interventions that reduce the risk of CKD progression and cardiovascular events might improve long-term outcomes, but high-quality evidence is insufficient. Novel models of post-discharge care after AKI that incorporate multidisciplinary health practitioners and leverage digital health technologies are being evaluated.[164]

Future prospects

Advances in identifying AKI subphenotypes, methods to leverage artificial intelligence and electronic health records, an improved understanding of the molecular pathways in human kidney disease, advanced statistical methodologies and clinical trial design, as well as development of new drugs show great promise in moving closer towards personalised AKI care.[123,165–169] Ongoing and future studies will further advance evidence on personalised treatment approaches (table 2). There is also increasing awareness that biological sex and gender affect susceptibility to AKI, leading to disparities in health care, especially in low-resource countries.[65] International collaboration, advocacy, and patient engagement are essential to overcome some of these challenges.

Declaration of interests

RJ has received funding from the Kidney Foundation of Canada Kidney Health Research Grant (855087-21KHRG). MJo has received consulting fees from Baxter, AM-Pharma, bioMérieux, SphingoTec, and AOP Health; declares honoraria for lectures from Baxter Healthcare Corp, AOP Health, and Biomerieux; and declares grants from Baxter and Fresenius received by the Medical University Innsbruck. MJa has received research funding from the Canadian Institutes for Health Research. ES declares an Investigator Initiated Research Grant (Acute Therapies) from Baxter received by the institution (Austin Health). MO and NL declare no competing interests.

References

1 Mehta RL, Burdmann EA, Cerdá J, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. *Lancet* 2016; **387:** 2017–25.
2 Hoste EAJ, Kellum JA, Selby NM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol* 2018; **14:** 607–25.
3 Ostermann M, Basu RK, Mehta RL. Acute kidney injury. *Intensive Care Med* 2023; **49:** 219–22.
4 Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). *Crit Care* 2013; **17:** 204.
5 Kellum JA, Sileanu FE, Bihorac A, Hoste EA, Chawla LS. Recovery after acute kidney injury. *Am J Respir Crit Care Med* 2017; **195:** 784–91.
6 Lameire NH, Levin A, Kellum JA, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. *Kidney Int* 2021; **100:** 516–26.
7 James MT, Levey AS, Tonelli M, et al. Incidence and prognosis of acute kidney diseases and disorders using an integrated approach to laboratory measurements in a universal health care system. *JAMA Netw Open* 2019; **2:** e191795.
8 Kellum JA, Sileanu FE, Murugan R, et al. Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol* 2015; **26:** 2231–38.
9 Vanmassenhove J, Steen J, Vansteelandt S, et al. The importance of the urinary output criterion for the detection and prognostic meaning of AKI. *Sci Rep* 2021; **11:** 11089.
10 Susantitaphong P, Cruz DN, Cerda J, et al. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 2013; **8:** 1482–93.
11 Smith TD, Soriano VO, Neyra JA, Chen J. Identifying KDIGO trajectory phenotypes associated with increased inpatient mortality. 2019. https://doi.org/10.1109/ichi.2019.8904739 (accessed Dec 6, 2024).
12 Mehta RL, Cerdá J, Burdmann EA, et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet* 2015; **385:** 2616–43.
13 Sawhney S, Bell S, Black C, et al. Harmonization of epidemiology of acute kidney injury and acute kidney disease produces comparable findings across four geographic populations. *Kidney Int* 2022; **101:** 1271–81.
14 See EJ, Polkinghorne KR, Toussaint ND, at al. Epidemiology and outcomes of acute kidney diseases: a comparative analysis. *Am J Nephrol* 2021; **52:** 342–50.
15 Pickering JW, Frampton CM, Walker RJ, Shaw GM, Endre ZH. Four hour creatinine clearance is better than plasma creatinine for monitoring renal function in critically ill patients. *Crit Care* 2012; **16:** R107.
16 de Oliveira Marques F, Oliveira SA, de Lima E Souza PF, et al. Kinetic estimated glomerular filtration rate in critically ill patients: beyond the acute kidney injury severity classification system. *Crit Care* 2017; **21:** 280.
17 Palsson R, Colona MR, Hoenig MP, et al. Assessment of interobserver reliability of nephrologist examination of urine sediment. *JAMA Netw Open* 2020; **3:** e2013959.
18 Chawla LS, Davison DL, Brasha-Mitchell E, et al. Development and standardization of a furosemide stress test to predict the severity of acute kidney injury. *Crit Care* 2013; **17:** R207.
19 Francis ST, Selby NM, Taal MW. Magnetic resonance imaging to evaluate kidney structure, function, and pathology: moving toward clinical application. *Am J Kidney Dis* 2023; **82:** 491–504.
20 Ostermann M, Legrand M, Meersch M, at al. Biomarkers in acute kidney injury. *Ann Intensive Care* 2024; **14:** 145.
21 Schunk SJ, Zarbock A, Meersch M, et al. Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study. *Lancet* 2019; **394:** 488–96.
22 Hoste E, Bihorac A, Al-Khafaji A, et al. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. *Intensive Care Med* 2020; **46:** 943–53.
23 Goldstein SL, Krallman KA, Roy JP, et al. Real-time acute kidney injury risk stratification-biomarker directed fluid management improves outcomes in critically ill children and young adults. *Kidney Int Rep* 2023; **8:** 2690–700.
24 Puthumana J, Ariza X, Belcher JM, at al. Urine interleukin 18 and lipocalin 2 are biomarkers of acute tubular necrosis in patients with cirrhosis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2017; **15:** 1003–13.e3.
25 Nadim MK, Kellum JA, Forni L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. *J Hepatol* 2024; **81:** 163–83.
26 Moledina DG, Obeid W, Smith RN, et al. Identification and validation of urinary CXCL9 as a biomarker for diagnosis of acute interstitial nephritis. *J Clin Invest* 2023; **133:** e168950.
27 Moledina DG, Wilson FP, Kukova L, et al. Urine interleukin-9 and tumor necrosis factor-α for prognosis of human acute interstitial nephritis. *Nephrol Dial Transplant* 2021; **36:** 1851–58.
28 Haines RW, Fowler AJ, Liang K, et al. Comparison of cystatin C and creatinine in the assessment of measured kidney function during critical illness. *Clin J Am Soc Nephrol* 2023; **18:** 997–1005.
29 Coca SG, Vasquez-Rios G, Mansour SG, et al. Plasma soluble tumor necrosis factor receptor concentrations and clinical events after hospitalization: findings from the ASSESS-AKI and ARID studies. *Am J Kidney Dis* 2023; **81:** 190–200.
30 Menez S, Wen Y, Xu L, et al. The ASSESS-AKI study found urinary epidermal growth factor is associated with reduced risk of major adverse kidney events. *Kidney Int* 2023; **104:** 1194–205.
31 Ostermann M, Zarbock A, Goldstein S, et al. Recommendations on acute kidney injury biomarkers from the Acute Disease Quality Initiative Consensus Conference: a consensus statement. *JAMA Netw Open* 2020; **3:** e2019209.

32 Ostermann M, Liu K. Pathophysiology of AKI. *Best Pract Res Clin Anaesthesiol* 2017; **31:** 305–14.

33 Desanti De Oliveira B, Xu K, Shen TH, et al. Molecular nephrology: types of acute tubular injury. *Nat Rev Nephrol* 2019; **15:** 599–612.

34 Peters E, Antonelli M, Wittebole X, et al. A worldwide multicentre evaluation of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from The Intensive Care Over Nations audit. *Crit Care* 2018; **22:** 188.

35 Zarbock A, Nadim MK, Pickkers P, et al. Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup. *Nat Rev Nephrol* 2023; **19:** 401–17.

36 Prowle JR, Forni LG, Bell M, et al. Postoperative acute kidney injury in adult non-cardiac surgery: joint consensus report of the Acute Disease Quality Initiative and PeriOperative Quality Initiative. *Nat Rev Nephrol* 2021; **17:** 605–18.

37 Zarbock A, Weiss R, Albert F, et al. Epidemiology of surgery associated acute kidney injury (EPIS-AKI): a prospective international observational multi-center clinical study. *Intensive Care Med* 2023; **49:** 1441–55.

38 Nishimoto M, Murashima M, Kokubu M, et al. Pre-operative proteinuria and post-operative acute kidney injury in noncardiac surgery: the NARA-Acute Kidney Injury cohort study. *Nephrol Dial Transplant* 2020; **35:** 2111–16.

39 Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. *N Engl J Med* 2018; **378:** 2263–74.

40 Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth* 2018; **121:** 706–21.

41 Futier E, Lefrant JY, Guinot PG, et al. Effect of individualized *vs* standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* 2017; **318:** 1346–57.

42 Legrand M, Falcone J, Cholley B, et al. Continuation vs discontinuation of renin-angiotensin system inhibitors before major noncardiac surgery: the Stop-or-Not randomized clinical trial. *JAMA* 2024; **332:** 970–78.

43 American Diabetes Association Professional Practice Committee. 16. Diabetes care in the hospital: standards of medical care in diabetes—2022. *Diabetes Care* 2022; **45** (suppl 1)**:** S244–53.

44 Baigent C, Emberson JR, Haynes R, et al. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022; **400:** 1788–801.

45 Packer M, Butler J, Zeller C, et al. Blinded withdrawal of long-term randomized treatment with empagliflozin or placebo in patients with heart failure. *Circulation* 2023; **148:** 1011–22.

46 Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, et al. Comparison of renal outcomes in off-pump versus on-pump coronary artery bypass grafting: a systematic review and meta-analysis of randomized controlled trials. *Nephrology* 2015; **20:** 727–35.

47 Garg AX, Devereaux PJ, Yusuf S, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. *JAMA* 2014; **311:** 2191–98.

48 Landoni G, Monaco F, Ti LK, et al. A randomized trial of intravenous amino acids for kidney protection. *N Engl J Med* 2024; **391:** 687–98.

49 Bell S, Rennie T, Marwick CA, Davey P. Effects of peri-operative nonsteroidal anti-inflammatory drugs on post-operative kidney function for adults with normal kidney function. *Cochrane Database Syst Rev* 2018; **11:** CD011274.

50 Mehta RL, Awdishu L, Davenport A, et al. Phenotype standardization for drug-induced kidney disease. *Kidney Int* 2015; **88:** 226–34.

51 Perazella MA, Rosner MH. Drug-induced acute kidney injury. *Clin J Am Soc Nephrol* 2022; **17:** 1220–33.

52 Perazella MA, Markowitz GS. Drug-induced acute interstitial nephritis. *Nat Rev Nephrol* 2010; **6:** 461–70.

53 Karimzadeh I, Barreto EF, Kellum JA, et al. Moving toward a contemporary classification of drug-induced kidney disease. *Crit Care* 2023; **27:** 435.

54 Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. *J Am Coll Cardiol* 2008; **52:** 1527–39.

55 Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol* 2022; **79:** 1757–80.

56 Fudim M, Loungani R, Doerfler SM, et al. Worsening renal function during decongestion among patients hospitalized for heart failure: findings from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial. *Am Heart J* 2018; **204:** 163–73.

57 Brisco MA, Zile MR, Hanberg JS, et al. Relevance of changes in serum creatinine during a heart failure trial of decongestive strategies: insights from the DOSE trial. *J Card Fail* 2016; **22:** 753–60.

58 Pitre T, Kiflen M, Helmeczi W, et al. The comparative effectiveness of vasoactive treatments for hepatorenal syndrome: a systematic review and network meta-analysis. *Crit Care Med* 2022; **50:** 1419–29.

59 Trakarnvanich T, Ngamvichchukorn T, Susantitaphong P. Incidence of acute kidney injury during pregnancy and its prognostic value for adverse clinical outcomes: a systematic review and meta-analysis. *Medicine* 2022; **101:** e29563.

60 Moronge D, Sullivan JC, Faulkner JL. Physiology of pregnancy-related acute kidney injury. *Compr Physiol* 2023; **13:** 4869–78.

61 Wiles K, Bramham K, Seed PT, at al. Serum creatinine in pregnancy: a systematic review. *Kidney Int Rep* 2018; **4:** 408–19.

62 El Minshawy O, Khedr MHS, Youssuf AM, at al. Value of the cell cycle arrest biomarkers in the diagnosis of pregnancy-related acute kidney injury. *Biosci Rep* 2021; **41:** BSR20200962.

63 Shields AD, Plante LA, Pacheco LD, Louis JM. Society for Maternal-Fetal Medicine Consult series #67: maternal sepsis. *Am J Obstet Gynecol* 2023; **229:** B2–19.

64 Banerjee A, Mehrotra G. Comparison of standard conservative treatment and early initiation of renal replacement therapy in pregnancy-related acute kidney injury: a single-center prospective study. *Indian J Crit Care Med* 2020; **24:** 688–94.

65 Dahiya A, Pannu N, Soranno DE. Sex as a biological variable in acute kidney injury. *Curr Opin Crit Care* 2023; **29:** 529–33.

66 Feng Y, Wang AY, Jun M, et al. Characterization of Risk prediction models for acute kidney injury: a systematic review and meta-analysis. *JAMA Netw Open* 2023; **6:** e2313359.

67 Ostermann M, Lumlertgul N, Wilson FP. Predictive models for acute kidney injury following cardiac surgery: the importance of accurate and actionable prediction. *JAMA* 2022; **327:** 927–29.

68 Uzendu A, Kennedy K, Chertow G, et al. Contemporary methods for predicting acute kidney injury after coronary intervention. *JACC Cardiovasc Interv* 2023; **16:** 2294–305.

69 Basu RK, Zappitelli M, Brunner L, et al. Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. *Kidney Int* 2014; **85:** 659–67.

70 Husain-Syed F, Ferrari F, Sharma A, et al. Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery. *Nephrol Dial Transplant* 2019; **34:** 308–17.

71 James MT, Hobson CE, Darmon M, et al. Applications for detection of acute kidney injury using electronic medical records and clinical information systems: workgroup statements from the 15(th) ADQI Consensus Conference. *Can J Kidney Health Dis* 2016; **3:** 9.

72 Selby NM, Casula A, Lamming L, et al. An organizational-level program of intervention for AKI: a pragmatic stepped wedge cluster randomized trial. *J Am Soc Nephrol* 2019; **30:** 505–15.

73 Wilson FP, Yamamoto Y, Martin M, et al. A randomized clinical trial assessing the effect of automated medication-targeted alerts on acute kidney injury outcomes. *Nat Commun* 2023; **14:** 2826.

74 Tome ACN, Ramalho RJ, Dos Santos KF, et al. Impact of an electronic alert in combination with a care bundle on the outcomes of acute kidney injury. *Diagnostics* 2022; **12**: 3121.

75 Wilson FP, Martin M, Yamamoto Y, et al. Electronic health record alerts for acute kidney injury: multicenter, randomized clinical trial. *BMJ* 2021; **372:** m4786.

76 Kashani KB, Awdishu L, Bagshaw SM, et al. Digital health and acute kidney injury: consensus report of the 27th Acute Disease Quality Initiative workgroup. 2023; **19**: 807–18.

77 James MT, Har BJ, Tyrrell BD, et al. Effect of clinical decision support with audit and feedback on prevention of acute kidney injury in patients undergoing coronary angiography: a randomized clinical trial. *JAMA* 2022; **328:** 839–49.

78 Macedo E, Hemmila U, Sharma SK, et al. Recognition and management of community-acquired acute kidney injury in low-resource settings in the ISN 0by25 trial: multi-country feasibility study. *PLoS Med* 2021; **18:** e1003408.

79 Goldstein SL, Krallman KA, Kirby C, et al. Integration of the renal angina index and urine neutrophil gelatinase-associated lipocalin improves severe acute kidney injury prediction in critically ill children and young adults. *Kidney Int Rep* 2022; **7:** 1842–49.

80 Göcze I, Jauch D, Götz M, et al. Biomarker-guided intervention to prevent acute kidney injury after major surgery: the prospective randomized BigpAK study. *Ann Surg* 2018; **267:** 1013–20.

81 Zarbock A, Küllmar M, Ostermann M, et al. Prevention of cardiac surgery-associated acute kidney injury by implementing the KDIGO guidelines in high-risk patients identified by biomarkers: the PrevAKI-Multicenter randomized controlled trial. *Anesth Analg* 2021; **133:** 292–302.

82 Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 2017; **43:** 1551–61.

83 See CY, Pan HC, Chen JY, et al. Improvement of composite kidney outcomes by AKI care bundles: a systematic review and meta-analysis. *Crit Care* 2023; **27:** 390.

84 Ostermann M, Chawla LS, Forni LG, et al. Drug management in acute kidney disease—report of the Acute Disease Quality Initiative XVI meeting. *Br J Clin Pharmacol* 2018; **84:** 396–403.

85 Beldhuis IE, Streng KW, Ter Maaten JM, et al. Renin-angiotensin system inhibition, worsening renal function, and outcome in heart failure patients with reduced and preserved ejection fraction: a meta-analysis of published study data. *Circ Heart Fail* 2017; **10:** e003588.

86 Hammond NE, Zampieri FG, Di Tanna GL, et al. Balanced crystalloids versus saline in critically ill adults—a systematic review with meta-analysis. *NEJM Evid* 2022; **1:** EVIDoa2100010.

87 Salerno F, Navickis RJ, Wilkes MM. Albumin infusion improves outcomes of patients with spontaneous bacterial peritonitis: a meta-analysis of randomized trials. *Clin Gastroenterol Hepatol* 2013; **11:** 123–30.e1.

88 Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; **367:** 1901–11.

89 Krzych ŁJ, Czempik PF. Impact of furosemide on mortality and the requirement for renal replacement therapy in acute kidney injury: a systematic review and meta-analysis of randomised trials. *Ann Intensive Care* 2019; **9:** 85.

90 Messina A, Calatroni M, Castellani G, et al. Understanding fluid dynamics and renal perfusion in acute kidney injury management. *J Clin Monit Comput* 2024; published online Aug 28. https://doi.org/10.1007/s10877-024-01209-3.

91 Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med* 2014; **370:** 1583–93.

92 Lamontagne F, Richards-Belle A, Thomas K, et al. Effect of reduced exposure to vasopressors on 90-day mortality in older critically ill patients with vasodilatory hypotension: a randomized clinical trial. *JAMA* 2020; **323:** 938–49.

93 De Backer D, Cecconi M, Chew MS, et al. A plea for personalization of the hemodynamic management of septic shock. *Crit Care* 2022; **26:** 372.

94 Busse LW, Ostermann M. Vasopressor therapy and blood pressure management in the setting of acute kidney injury. *Semin Nephrol* 2019; **39:** 462–72.

95 Tumlin JA, Murugan R, Deane AM, et al. Outcomes in patients with vasodilatory shock and renal replacement therapy treated with intravenous angiotensin II. *Crit Care Med* 2018; **46:** 949–57.

96 Powell-Tuck J, Crichton S, Raimundo M, at al. Anaemia is not a risk factor for progression of acute kidney injury: a retrospective analysis. *Crit Care* 2016; **20:** 52.

97 Garg AX, Badner N, Bagshaw SM, et al. Safety of a restrictive versus liberal approach to red blood cell transfusion on the outcome of aki in patients undergoing cardiac surgery: a randomized clinical trial. *J Am Soc Nephrol* 2019; **30:** 1294–304.

98 Lee ZY, Dresen E, Lew CCH, et al. The effects of higher versus lower protein delivery in critically ill patients: an updated systematic review and meta-analysis of randomized controlled trials with trial sequential analysis. *Crit Care* 2024; **28:** 15.

99 Fiaccadori E, Sabatino A, Barazzoni R, et al. ESPEN guideline on clinical nutrition in hospitalized patients with acute or chronic kidney disease. *Clin Nutr* 2021; **40:** 1644–68.

100 Gaudry S, Hajage D, Schortgen F, et al. Initiation strategies for renal-replacement therapy in the intensive care unit. *N Engl J Med* 2016; **375:** 122–33.

101 Barbar SD, Clere-Jehl R, Bourredjem A, et al. Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. *N Engl J Med* 2018; **379:** 1431–42.

102 Bagshaw SM, Wald R, Adhikari NKJ, et al. Timing of initiation of renal-replacement therapy in acute kidney injury. *N Engl J Med* 2020; **383:** 240–51.

103 Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA* 2016; **315:** 2190–99.

104 Gaudry S, Hajage D, Martin-Lefevre L, et al. Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open-label, randomised, controlled trial. *Lancet* 2021; **397:** 1293–300.

105 Ostermann M, Bagshaw SM, Lumlertgul N, Wald R. Indications for and timing of initiation of KRT. *Clin J Am Soc Nephrol* 2023; **18:** 113–20.

106 Ostermann M, Ankawi G, Cantaluppi V, et al. Nomenclature of extracorporeal blood purification therapies for acute indications: the nomenclature standardization conference. *Blood Purif* 2024; **53:** 358–72.

107 Bagshaw SM, Neyra JA, Tolwani AJ, Wald R. Debate: intermittent hemodialysis versus continuous kidney replacement therapy in the critically ill patient: the argument for CKRT. *Clin J Am Soc Nephrol* 2023; **18:** 647–60.

108 Wald R, Gaudry S, da Costa BR, et al. Initiation of continuous renal replacement therapy versus intermittent hemodialysis in critically ill patients with severe acute kidney injury: a secondary analysis of STARRT-AKI trial. *Intensive Care Med* 2023; **49:** 1305–16.

109 Ostermann M, Joannidis M, Pani A, et al. Patient selection and timing of continuous renal replacement therapy. *Blood Purif* 2016; **42:** 224–37.

110 Wald R, Beaubien-Souligny W, Chanchlani R, et al. Delivering optimal renal replacement therapy to critically ill patients with acute kidney injury. *Intensive Care Med* 2022; **48:** 1368–81.

111 Bellomo R, Cass A, Cole L, et al. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med* 2009; **361:** 1627–38.

112 Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med* 2008; **359:** 7–20.

113 Chawla LS. Permissive azotemia during acute kidney injury enables more rapid renal recovery and less renal fibrosis: a hypothesis and clinical development plan. *Crit Care* 2022; **26:** 116.

114 Murugan R, Bellomo R, Palevsky PM, Kellum JA. Ultrafiltration in critically ill patients treated with kidney replacement therapy. *Nat Rev Nephrol* 2021; **17:** 262–76.

115 Zarbock A, Küllmar M, Kindgen-Milles D, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury: a randomized clinical trial. *JAMA* 2020; **324:** 1629–39.

116 Jacobs R, Verbrugghe W, Dams K, et al. Regional citrate anticoagulation in continuous renal replacement therapy: is metabolic fear the enemy of logic? A systematic review and meta-analysis of randomised controlled trials. *Life*2023; **13:** 1198.

117 Katulka RJ, Al Saadon A, Sebastianski M, et al. Determining the optimal time for liberation from renal replacement therapy in critically ill patients: a systematic review and meta-analysis (DOnE RRT). *Crit Care* 2020; **24:** 50.

118 van der Voort PH, Boerma EC, Koopmans M, et al. Furosemide does not improve renal recovery after hemofiltration for acute renal failure in critically ill patients: a double blind randomized controlled trial. *Crit Care Med* 2009; **37:** 533–38.

119 Roberts JA, Joynt GM, Lee A, et al. The effect of renal replacement therapy and antibiotic dose on antibiotic concentrations in critically ill patients: data from the Multinational Sampling Antibiotics in Renal Replacement Therapy Study. *Clin Infect Dis* 2021; **72:** 1369–78.

120 Gordon AC, Alipanah-Lechner N, Bos LD, et al. From ICU syndromes to ICU subphenotypes: consensus report and recommendations for developing precision medicine in the ICU. *Am J Respir Crit Care Med* 2024; **210:** 155–66.

121 Birkelo BC, Koyner JL, Ostermann M, Bhatraju PK. The road to precision medicine for acute kidney injury. *Crit Care Med* 2024; **52:** 1127–37.

122 Legrand M, Bagshaw SM, Bhatraju PK, et al. Sepsis-associated acute kidney injury: recent advances in enrichment strategies, sub-phenotyping and clinical trials. *Crit Care* 2024; **28:** 92.

123 Bhatraju PK, Zelnick LR, Herting J, et al. Identification of acute kidney injury subphenotypes with differing molecular signatures and responses to vasopressin therapy. *Am J Respir Crit Care Med* 2019; **199:** 863–72.

124 Pickkers P, Darmon M, Hoste E, et al. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intensive Care Med* 2021; **47:** 835–50.

125 Monard C, Meersch-Dini M, Joannidis M. When the kidneys hurt, the other organs suffer. *Intensive Care Med* 2023; **49:** 233–36.

126 Jensen SK, Heide-Jørgensen U, Gammelager H, Birn H, Christiansen CF. Acute kidney injury duration and 20-year risks of CKD and cardiovascular disease. *Kidney Int Rep* 2024; **9:** 817–29.

127 James MT, Bhatt M, Pannu N, Tonelli M. Long-term outcomes of acute kidney injury and strategies for improved care. *Nat Rev Nephrol* 2020; **16:** 193–205.

128 Mayer KP, Ortiz-Soriano VM, Kalantar A, et al. Acute kidney injury contributes to worse physical and quality of life outcomes in survivors of critical illness. *BMC Nephrol* 2022; **23:** 137.

129 Grams ME, Matsushita K, Sang Y, et al. Explaining the racial difference in AKI incidence. *J Am Soc Nephrol* 2014; **25:** 1834–41.

130 Holmes J, Phillips D, Donovan K, Geen J, Williams JD, Phillips AO. Acute kidney injury, age, and socioeconomic deprivation: evaluation of a national data set. *Kidney Int Rep* 2019; **4:** 824–32.

131 Forni LG, Darmon M, Ostermann M, et al. Renal recovery after acute kidney injury. *Intensive Care Med* 2017; **43:** 855–66.

132 Chawla LS, Bellomo R, Bihorac A, et al. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 2017; **13:** 241–57.

133 Siew ED, Abdel-Kader K, Perkins AM, et al. Timing of recovery from moderate to severe aki and the risk for future loss of kidney function. *Am J Kidney Dis* 2020; **75:** 204–13.

134 Bhatraju PK, Zelnick LR, Chinchilli VM, et al. Association between early recovery of kidney function after acute kidney injury and long-term clinical outcomes. *JAMA Netw Open* 2020; **3:** e202682.

135 Siew ED, Parr SK, Abdel-Kader K, et al. Predictors of recurrent AKI. *J Am Soc Nephrol* 2016; **27:** 1190–200.

136 Liu KD, Yang J, Tan TC, et al. Risk factors for recurrent acute kidney injury in a large population-based cohort. *Am J Kidney Dis* 2019; **73:** 163–73.

137 See EJ, Jayasinghe K, Glassford N, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. *Kidney Int* 2019; **95:** 160–72.

138 Haines RW, Powell-Tuck J, Leonard H, Crichton S, Ostermann M. Long-term kidney function of patients discharged from hospital after an intensive care admission: observational cohort study. *Sci Rep* 2021; **11:** 9928.

139 Muiru AN, Hsu JY, Zhang X, et al. Risk for chronic kidney disease progression after acute kidney injury: findings from the chronic renal insufficiency cohort study. *Ann Intern Med* 2023; **176:** 961–68.

140 See EJ, Toussaint ND, Bailey M, et al. Risk factors for major adverse kidney events in the first year after acute kidney injury. *Clin Kidney J* 2019; **14:** 556–63.

141 De Corte W, Dhondt A, Vanholder R, et al. Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a prospective cohort study. *Crit Care* 2016; **20:** 256.

142 Parr SK, Matheny ME, Abdel-Kader K, et al. Acute kidney injury is a risk factor for subsequent proteinuria. *Kidney Int* 2018; **93:** 460–69.

143 Hsu CY, Chinchilli VM, Coca S, et al. Post-acute kidney injury proteinuria and subsequent kidney disease progression: the Assessment, Serial Evaluation, and Subsequent Sequelae in Acute Kidney Injury (ASSESS-AKI) study. *JAMA Intern Med* 2020; **180:** 402–10.

144 Silver SA, Harel Z, McArthur E, et al. Causes of death after a hospitalization with AKI. *J Am Soc Nephrol* 2018; **29:** 1001–10.

145 McNicholas B, Akcan Arikan A, Ostermann M. Quality of life after acute kidney injury. *Curr Opin Crit Care* 2023; **29:** 566–79.

146 Villeneuve PM, Clark EG, Sikora L, Sood MM, Bagshaw SM. Health-related quality-of-life among survivors of acute kidney injury in the intensive care unit: a systematic review. *Intensive Care Med* 2016; **42:** 137–46.

147 Go AS, Hsu CY, Yang J, et al. Acute kidney injury and risk of heart failure and atherosclerotic events. *Clin J Am Soc Nephrol* 2018; **13:** 833–41.

148 James MT, Ghali WA, Knudtson ML, et al. Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography. *Circulation* 2011; **123:** 409–16.

149 Wu VC, Wu PC, Wu CH, et al. The impact of acute kidney injury on the long-term risk of stroke. *J Am Heart Assoc* 2014; **3:** e000933.

150 Tsai HH, Yen RF, Lin CL, Kao CH. Increased risk of dementia in patients hospitalized with acute kidney injury: a nationwide population-based cohort study. *PLoS One* 2017; **12:** e0171671.

151 Lai TS, Wang CY, Pan SC, et al. Risk of developing severe sepsis after acute kidney injury: a population-based cohort study. *Crit Care* 2013; **17:** R231.

152 Wu PC, Wu CJ, Lin CJ, Wu VC. Long-term risk of upper gastrointestinal hemorrhage after advanced AKI. *Clin J Am Soc Nephrol* 2015; **10:** 353–62.

153 Wang WJ, Chao CT, Huang YC, et al. The impact of acute kidney injury with temporary dialysis on the risk of fracture. *J Bone Miner Res* 2014; **29:** 676–84.

154 Chao CT, Wang CY, Lai CF, et al. Dialysis-requiring acute kidney injury increases risk of long-term malignancy: a population-based study. *J Cancer Res Clin Oncol* 2014; **140:** 613–21.

155 Acute Kidney Injury Work Group KDIGO. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group KDIGO clinical practice guideline for acute kidney injury. *Kidney Inter* **2:** 1–138.

156 Thanapongsatorn P, Chaikomon K, Lumlertgul N, et al. Comprehensive versus standard care in post-severe acute kidney injury survivors, a randomized controlled trial. *Crit Care* 2021; **25:** 322.

157 Brar S, Ye F, James MT, Harrison TG, Pannu N. Processes of care after hospital discharge for survivors of acute kidney injury: a population-based cohort study. *Am J Kidney Dis* 2024; **83:** 216–28.

158 Siew ED, Liu KD, Bonn J, et al. Improving care for patients after hospitalization with AKI. *J Am Soc Nephrol* 2020; **31:** 2237–41.

159 Silver SA, Saragosa M, Adhikari NK, et al. What insights do patients and caregivers have on acute kidney injury and posthospitalisation care? A single-centre qualitative study from Toronto, Canada. *BMJ Open* 2018; **8:** e021418.

160 Phipps DL, Morris RL, Blakeman T, Ashcroft DM. What is involved in medicines management across care boundaries? A qualitative study of healthcare practitioners' experiences in the case of acute kidney injury. *BMJ Open* 2017; **7:** e011765.

161 Puthumana J, Thiessen-Philbrook H, Xu L, et al. Biomarkers of inflammation and repair in kidney disease progression. *J Clin Invest* 2021; **131:** e139927.

162 James MT, Pannu N, Hemmelgarn BR, et al. Derivation and external validation of prediction models for advanced chronic kidney disease following acute kidney injury. *JAMA* 2017; **318:** 1787–97.

163 Sawhney S, Tan Z, Black C, et al. Validation of risk prediction models to inform clinical decisions after acute kidney injury. *Am J Kidney Dis* 2021; **78:** 28–37.

164 Adebe K. A patient-centered trial of a process-of-care intervention in hospitalized aki patients: the COPE-AKI Trial (COPE-AKI). 2023. https://cope-akistudy.pitt.edu (accessed Dec 7, 2024).

165 Gordon AC, Alipanah-Lechner N, Bos LD, et al. From ICU Syndromes to ICU subphenotypes: consensus report and recommendations for developing precision medicine in the ICU. *Am J Respir Crit Care Med* 2024; **210:** 155–66.

166 Pickkers P, Murray PT, Ostermann M. New drugs for acute kidney injury. *Intensive Care Med* 2022; **48:** 1796–98.

167 Zarbock A, Forni LG, Koyner JL, et al. Recommendations for clinical trial design in acute kidney injury from the 31st acute disease quality initiative consensus conference. A consensus statement. *Intensive Care Med* 2024; **50:** 1426–37.

168 von Groote T, Meersch M, Romagnoli S, et al. Biomarker-guided intervention to prevent acute kidney injury after major surgery (BigpAK-2 trial): study protocol for an international, prospective, randomised controlled multicentre trial. *BMJ Open* 2023; **13:** e070240.

169 Zappalà S, Alfieri F, Ancona A, et al. Development and external validation of a machine learning model for the prediction of persistent acute kidney injury stage 3 in multi-centric, multi-national intensive care cohorts. *Crit Care* 2024; **28:** 189.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.